

(FILE 'HOME' ENTERED AT 11:49:28 ON 18 MAR 2003)

FILE 'BIOSIS, MEDLINE, CAPLUS, EMBASE, CANCERLIT' ENTERED AT 11:49:39 ON  
18 MAR 2003

L1	1374	PHOSPHATE REABSORPTION
L2	0	PHOSHPATE RE-ABSORPTION
L3	10	FRP-4
L4	371	FRIZZLED RELATED PROTEIN
L5	6	FRZB2
L6	2	DDC4
L7	0	L1 AND L3
L8	0	L1 AND L4
L9	0	L1 AND L5
L10	0	L1 AND L6
L11	79	PHOSPHATONIN
L12	11	L11 AND L1
L13	4	DUP REM L12 (7 DUPLICATES REMOVED)
L14	3630	FRP
L15	1	L1 AND L14
L16	1297	PHOSPHATURIC
L17	154	L1 AND L16
L18	1	L3 AND L16
L19	4	L4 AND L16
L20	2	DUP REM L19 (2 DUPLICATES REMOVED)
L21	0	L5 AND L16
L22	0	L6 AND L16

L13 ANSWER 1 OF 4 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 1  
ACCESSION NUMBER: 2002:478909 BIOSIS  
DOCUMENT NUMBER: PREV200200478909  
TITLE: Fibroblast growth factor (FGF)-23 inhibits renal

**phosphate reabsorption** by activation of  
the mitogen-activated protein kinase pathway.

AUTHOR(S): Yamashita, Tetsuo; Konishi, Morichika; Miyake, Ayumi; Inui,  
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CORPORATE SOURCE: (1) Department of Genetic Biochemistry, Graduate School of  
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SOURCE: Journal of Biological Chemistry, (August 2, 2002) Vol. 277,  
No. 31, pp. 28265-28270. <http://www.jbc.org/>. print.  
ISSN: 0021-9258.

DOCUMENT TYPE: Article

LANGUAGE: English

AB The homeostasis of the plasma phosphate level is essential for many  
biological processes including skeletal mineralization. The reabsorption  
of phosphate in the kidney is a major determinant of the plasma levels of  
phosphate. **Phosphatonin** is a hormone-like factor that  
specifically inhibits phosphate uptake in renal proximal epithelial cells.  
Recent studies on tumor-induced osteomalacia suggested that  
**phosphatonin** was potentially identical to fibroblast growth factor  
(FGF)-23. However, as purified recombinant FGF-23 could not inhibit  
phosphate uptake in renal proximal epithelial cells, the mechanism of  
action of FGF-23 remains to be elucidated. Therefore, we examined the  
mechanism of action of FGF-23 in cultured renal proximal epithelial cells,  
opossum kidney cells. FGF-23 was found to require heparin-like molecules  
for its inhibitory activity on phosphate uptake. FGF-23 binds to the FGF  
receptor 3c, which is mainly expressed in opossum kidney cells, with high  
affinity. An inhibitor for tyrosine kinases of the FGF receptor, SU 5402,  
blocked the activity of FGF-23. FGF-23 activated the mitogen-activated  
protein kinase (MAPK) pathway, which is the major intracellular signaling  
pathway of FGF. Inhibitors of the MAPK pathway, PD98059 and SB203580, also  
blocked the activity of FGF-23. The present findings have revealed a novel  
MAPK-dependent mechanism of the regulation of phosphate uptake by FGF  
signaling.

L13 ANSWER 2 OF 4 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 2  
ACCESSION NUMBER: 2001:383764 BIOSIS  
DOCUMENT NUMBER: PREV200100383764  
TITLE: FGF-23 inhibits renal tubular phosphate transport and is a

PHEX substrate.

AUTHOR(S): Bowe, Ann E.; Finnegan, Richard; de Beur, Suzanne M. Jan;  
Cho, Justin; Levine, Michael A.; Kumar, Rajiv; Schiavi,  
Susan C. (1)

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SOURCE: Biochemical and Biophysical Research Communications, (June  
22, 2001) Vol. 284, No. 4, pp. 977-981. print.  
ISSN: 0006-291X.

DOCUMENT TYPE: Article

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Oncogenic osteomalacia (OOM), X-linked hypophosphatemia (XLH), and  
autosomal dominant hypophosphatemic rickets (ADHR) are phenotypically  
similar disorders characterized by hypophosphatemia, decreased renal  
**phosphate reabsorption**, normal or low serum calcitriol  
concentrations, normal serum concentrations of calcium and parathyroid  
hormone, and defective skeletal mineralization. XLH results from mutations  
in the PHEX gene, encoding a membrane-bound endopeptidase, whereas ADHR is  
associated with mutations of the gene encoding FGF-23. Recent evidence  
that FGF-23 is expressed in mesenchymal tumors associated with OOM  
suggests that FGF-23 is responsible for the phosphaturic activity

previously termed "**phosphatonin**." Here we show that both wild-type FGF-23 and the ADHR mutant, FGF-23(R179Q), inhibit phosphate uptake in renal epithelial cells. We further show that the endopeptidase, PHEX, degrades native FGF-23 but not the mutant form. Our results suggest that FGF-23 is involved in the pathogenesis of these three hypophosphatemic disorders and directly link PHEX and FGF-23 within the same biochemical pathway.

L13 ANSWER 3 OF 4 MEDLINE  
 ACCESSION NUMBER: 2002053124 MEDLINE  
 DOCUMENT NUMBER: 21637562 PubMed ID: 11778363  
 TITLE: [Familial hypophosphatemic rickets].  
 Familiaris hypophosphataemias rachitis.  
 AUTHOR: Reusz G  
 CORPORATE SOURCE: Altalanos Orvostudományi Kar, I. sz. Gyermekklinika,  
 Semmelweis Egyetem, Budapest.. reusz@gyer1.sote.hu  
 SOURCE: ORVOSI HETILAP, (2001 Dec 2) 142 (48) 2659-65. Ref: 41  
 Journal code: 0376412. ISSN: 0030-6002.  
 PUB. COUNTRY: Hungary  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 General Review; (REVIEW)  
 (REVIEW, TUTORIAL)  
 LANGUAGE: Hungarian  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200204  
 ENTRY DATE: Entered STN: 20020125  
 Last Updated on STN: 20020405  
 Entered Medline: 20020404

AB Familial hypophosphatemic rickets (FHR) is characterized by isolated defect of renal **phosphate reabsorption**, hypophosphataemia, rickets and poor growth. In untreated cases parathyroid hormone and calcitriol levels are normal. FHR is caused by mutations of the PHEX gene encoding a zinc-binding metalloprotease enzyme. PHEX is expressed in bones and the parathyroid gland but not in the kidney. The gene product is involved in the inactivation of a phosphate regulating hormone (**phosphatonin**). The presence of this hormone through unknown mechanisms decreases the sodium-dependent phosphate cotransporter in the kidney resulting in impaired phosphate transport. In addition the PHEX gene product exerts autocrine and paracrine effects on the bone. Despite recent advances in the understanding of the pathomechanism, treatment of FHR is still symptomatic. It consists of active vitamin D analogues and oral phosphate supplementation. Nephrocalcinosis is a well-known, usually non-progressive side effect of the conventional therapy. As shown by pilot studies, poorly growing children with FHR may benefit from the positive effect of human recombinant growth hormone (rhGH). However, rhGH treatment could aggravate the already existing tendency to disproportionate growth resulting in the overgrowth of the trunk. The disturbed phosphate homeostasis persists during the whole life span of the FHR patients. It is therefore essential to provide lifelong care, to prevent late skeletal and dental consequences or to treat them if already established. That care should be done by the teamwork of the pediatrician, internist, orthopedist, dentist and the psychologist.

L13 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 2001:580342 CAPLUS  
 DOCUMENT NUMBER: 135:286097  
 TITLE: Molecular aspects of phosphate homeostasis in mammals  
 AUTHOR(S): Beck, L.; Silve, C.  
 CORPORATE SOURCE: INSERM U 426 et Institut federatif de recherche  
 .mchlt. Cellules Epitheliales .mchgt., Faculte de  
 medecine Xavier Bichat, Paris, Fr.  
 SOURCE: Nephrologie (2001), 22(4), 149-159  
 CODEN: NEPHDY; ISSN: 0250-4960  
 PUBLISHER: Medecine et Hygiene

DOCUMENT TYPE: Journal; General Review  
LANGUAGE: French

AB A review with refs. Renal **phosphate reabsorption**, the major determinant of phosphate homeostasis, is primarily dependent on dietary phosphate content and multiple hormonal factors. Over the last few years, the identification of sodium-dependent phosphate transporters in kidney, intestine and bone, as well as new insights into the mol. mechanisms involved in several hereditary hypophosphatemias, allow to set up novel **phosphate reabsorption** regulatory pathways. This review describes mol. players involved in these mechanisms, summarizes phosphate transport data in kidney, intestine and bone, and describes recent findings concerning the three most common hereditary hypophosphatemias.

REFERENCE COUNT: 76 THERE ARE 76 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 1 OF 1 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.  
 ACCESSION NUMBER: 75063246 EMBASE  
 DOCUMENT NUMBER: 1975063246  
 TITLE: Mechanism of the blunted phosphaturia in saline loaded  
 thyroparathyroidectomized dogs.  
 AUTHOR: Beck L.H.; Goldberg M.  
 CORPORATE SOURCE: Ren. Electrol. Sect., Dept. Med., Univ. Pennsylvania Sch.  
 Med., Philadelphia, Pa., United States  
 SOURCE: Kidney International, (1974) 6/1 (18-23).  
 CODEN: KDYIA5  
 DOCUMENT TYPE: Journal  
 FILE SEGMENT: 037 Drug Literature Index  
 028 Urology and Nephrology  
 003 Endocrinology  
 LANGUAGE: English

AB To define the relationships between sodium and phosphate transport in the presence and absence of parathyroid hormone (PTH), and to evaluate the effects of saline loading on these relationships, recollection micropuncture studies were done in proximal tubules of intact and thyroparathyroidectomized (TPTX) dogs. Micropuncture collections were made before and after 5% of body wt saline expansion (SE) in three groups of dogs: intact (N=6), acute TPTX (N=6) and 24 hr TPTX (N=6). Before SE, proximal tubular fluid/ultrafiltrate phosphate ratio [(TF/UF)p] was  $0.62 \pm 0.05$  in intact dogs and was unrelated to tubular fluid/plasma inulin ratio [(TF/P)In]. In both TPTX groups (TF/UF)p varied inversely with (TF/P)In ( $P < 0.001$ ). In late proximal tubules [(TF/P)In  $> 1.70$ ], (TF/UF)p was 0.39 in acute TPTX and 0.40 in 24 hr TPTX. After SE, (TF/UF)p rose to values of 0.7 to 0.8 in all three groups. (TF/P)In fell in all animals after SE so that fractional reabsorption of phosphate (**FRP**) in the proximal tubule fell markedly. The decrement in **FRP** was equivalent in all three groups: 0.29 in intact, 0.34 in acute TPTX and 0.34 in 24 hr TPTX. A significant phosphaturia (0.26 of filtered load) occurred only in intact animals, despite equivalent natriuresis in all three groups. The authors conclude that SE causes equivalent inhibition of proximal **phosphate reabsorption** in both intact and TPTX dogs. In intact dogs, the portion of proximal tubular phosphate inhibited by SE is almost totally excreted. In TPTX animals, enhanced **phosphate reabsorption** beyond the cortical proximal tubule accounts for the blunted phosphaturia.

L18 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:461775 CAPLUS

DOCUMENT NUMBER: 137:276731

TITLE: Tumors associated with oncogenic osteomalacia express genes important in bone and mineral metabolism

AUTHOR(S): Jan De Beur, Suzanne M.; Finnegan, Richard B.; Vassiliadis, John; Cook, Brian; Barberio, Dana; Estes, Scott; Manavalan, Partha; Petroziello, Joseph; Madden, Stephen L.; Cho, Justin Y.; Kumar, Rajiv; Levine, Michael A.; Schiavi, Susan C.

CORPORATE SOURCE: Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA

SOURCE: Journal of Bone and Mineral Research (2002), 17(6), 1102-1110

CODEN: JBMREJ; ISSN: 0884-0431

PUBLISHER: American Society for Bone and Mineral Research

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Oncogenic osteomalacia (OOM) is assocd. with primitive mesenchymal tumors that secrete **phosphaturic** factors resulting in low serum concns. of phosphate and calcitriol, phosphaturia, and defective bone mineralization. To identify overexpressed genes in these tumors, the authors compared gene expression profiles of tumors resected from patients with OOM and histol. similar control tumors using serial anal. of gene expression (SAGE). Three hundred and sixty-four genes were expressed at least twofold greater in OOM tumors compared with control tumors. A subset of 67 highly expressed genes underwent validation with an extended set of OOM and control tumors using array anal. or reverse-transcription polymerase chain reaction (RT-PCR). Ten of these validated genes were consistently overexpressed in all OOM tumors relative to control tumors. Strikingly, genes with roles in bone matrix formation, mineral ion transport, and bone mineralization were highly expressed in the OOM tumors.

L20 ANSWER 1 OF 2 MEDLINE DUPLICATE 1  
 ACCESSION NUMBER: 2002430237 MEDLINE  
 DOCUMENT NUMBER: 22174470 PubMed ID: 12187320  
 TITLE: New insights into phosphate homeostasis: fibroblast growth factor 23 and **frizzled-related protein-4** are **phosphaturic** factors derived from tumors associated with osteomalacia.  
 AUTHOR: Kumar Rajiv  
 CORPORATE SOURCE: Department of Internal Medicine, Mayo Clinic and Foundation, Rochester, Minnesota 55905, USA..  
 rkumar@mayo.edu  
 CONTRACT NUMBER: AR27032 (NIAMS)  
 DK25409 (NIDDK)  
 DK58546 (NIDDK)  
 DK59505 (NIDDK)  
 SOURCE: CURRENT OPINION IN NEPHROLOGY AND HYPERTENSION, (2002 Sep) 11 (5) 547-53. Ref: 78  
 Journal code: 9303753. ISSN: 1062-4821.  
 PUB. COUNTRY: England: United Kingdom  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 General Review; (REVIEW)  
 (REVIEW, TUTORIAL)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200302  
 ENTRY DATE: Entered STN: 20020821  
 Last Updated on STN: 20030222  
 Entered Medline: 20030221  
 AB PURPOSE OF REVIEW: Studies of patients with tumors associated with osteomalacia (tumor-induced osteomalacia), X-linked hypophosphatemia (XLH) and autosomal-dominant hypophosphatemic rickets have provided important new insights into the identity and mechanisms of action of factors that play a role in controlling renal phosphate excretion and serum phosphate concentrations. In the present review I discuss how these disorders may be mechanistically related to one another. RECENT FINDINGS: Patients (or mice) with these disorders manifest rickets as a result of excessive urinary phosphate losses. Tumors associated with osteomalacia elaborate factors ('phosphatonins') that increase renal phosphate excretion and reduce serum phosphate concentrations. These factors include fibroblast growth factor (FGF) 23 and **frizzled-related protein-4**. Mice with XLH (Hyp) elaborate a circulating factor that induces changes in mineral metabolism similar to those in patients with tumor-induced osteomalacia. In mice and humans with XLH, a mutant enzyme, **phex/PHEX**, cannot degrade the **phosphaturic** factor. Patients with autosomal-dominant hypophosphatemic rickets produce a mutant FGF 23 that is resistant to proteolytic degradation. Excessive FGF 23 activity is associated with increased renal phosphate excretion and hypophosphatemia. SUMMARY: In tumor-induced osteomalacia, excessive production of factors such as FGF 23 and **frizzled-related protein** -4 is associated with inability of endogenous proteolytic enzymes to degrade these individual substances, with resultant hyperphosphaturia, hypophosphatemia, and rickets. In XLH, mutant **PHEX/phex** (phosphate-regulating gene with homology to endopeptidases located on the X-chromosome) activity prevents degradation of a **phosphaturic** factor. In autosomal-dominant hypophosphatemic rickets, a mutant form of FGF 23 that is resistant to proteolytic degradation causes increased renal phosphate losses and hypophosphatemia.

L20 ANSWER 2 OF 2 MEDLINE DUPLICATE 2  
 ACCESSION NUMBER: 2002359281 MEDLINE  
 DOCUMENT NUMBER: 22097723 PubMed ID: 12105393  
 TITLE: Phosphatonins: a new class of phosphate-regulating proteins.  
 AUTHOR: Schiavi Susan C; Moe Orson W

CORPORATE SOURCE: Applied Genomics, Genzyme Corporation, One Mountain Road,  
Framingham, Massachusetts 01701, USA..  
susan.schiavi@genzyme.com  
CONTRACT NUMBER: P01-DK20543 (NIDDK)  
R01-48482  
R01-54396  
SOURCE: CURRENT OPINION IN NEPHROLOGY AND HYPERTENSION, (2002 Jul)  
11 (4) 423-30. Ref: 72  
Journal code: 9303753. ISSN: 1062-4821.  
PUB. COUNTRY: England: United Kingdom  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
(REVIEW, TUTORIAL)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200212  
ENTRY DATE: Entered STN: 20020710  
Last Updated on STN: 20021217  
Entered Medline: 20021204

AB PURPOSE OF REVIEW: There is an intimate relationship between phosphate and calcium homeostasis throughout the animal kingdom. One traditional assumption is that all phosphate-regulating hormones are primarily calcium-regulating hormones. Although the notion of a circulating substance dedicated to phosphate homeostasis has existed for more than a decade, it is not until recently that these hormones have been identified. The molecular characterization of these substances will prove to be critical for understanding phosphate physiology and clinical disorders of phosphate metabolism. RECENT FINDINGS: This review will focus primarily on the first two proteins recently shown to have phosphatonin properties. Using three human diseases as models and a combination of positional cloning and differential gene expression, fibroblast growth factor 23 and **frizzled-related protein 4** were shown to be associated with one or more of these diseases. Although both of these substances have **phosphaturic** action, their biological effects are likely to extend beyond epithelial phosphate transport. SUMMARY: The phosphatonins are a growing family of substances that may act on multiple organs in autocrine, paracrine, and endocrine modes to regulate phosphate metabolism. As this list expands, the need for a more rigid definition of the term phosphatonin becomes evident. The identification and characterization of these phosphate-regulatory compounds will provide a clearer understanding of how individual phosphatonins regulate phosphate in normal and disease physiology.